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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,814	07/26/2001	Madeline M. Butler	ISPH-0587	6393

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/915,814	Butler et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 16, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 4-83* is/are pending in the application.

4a) Of the above, claim(s) *16-70* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-15, and 71-83* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed May 16, 2003, Paper No. 12.

Claims 1, 2, 4-83 are pending in the instant application.

Any rejections not repeated in this Office action are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

This application contains claims 16-70 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Maintained Rejections

Claims 71 is rejected under 35 U.S.C. 112, first paragraph, for lacking adequate written description, for the reasons of record set forth in the Office action mailed January 14, 2003, Paper No. 8.

Applicant's arguments filed May 16, 2003 have been fully considered but they are not persuasive. Applicants argue that adequate disclosure describing alternatively spliced forms of human hormone sensitive lipase has been provided in the specification, and that SEQ ID NO: 17, the Holst et al reference has been cited and example 15 describe an alternatively spliced form of

hormone sensitive lipase, thereby providing adequate written description for claim 71. Contrary to Applicant's assertions, the description of a single species within the genus comprising any and/or all alternatively spliced forms of hormone sensitive lipase does adequately describe the broad genus claimed. The possibility that overlapping sequences exist in alternatively spliced forms of hsl does not compensate for the failure to disclose what those alternative sequences are. The genus reads on numerous structural variants that are not disclosed in the instant specification and therefore the rejection for lack of adequate written description is maintained.

Claim 71 is rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office action mailed January 14, 2003, Paper No. 8.

Applicants' arguments filed May 16, 2003 have been fully considered but they are not persuasive. Applicants argue that it would not require undue experimentation to design and assess antisense to be used to inhibit the expression of any and/or all alternatively spliced forms of hsl because an alternatively spliced sequence has been disclosed in the specification for hsl. Contrary to Applicants' assertions, the disclosure of a single alternatively spliced form of hsl does not enable one to design and assess antisense for inhibiting any and/or all alternatively spliced isoforms of hsl. It would require undue experimentation beyond that which has been taught in the instant disclosure to determine the nucleotide sequences of all alternatively spliced isoforms of hsl, and then to design antisense to inhibit these isoforms. The delineation of a single species does not

enable the broad genus drawn to any and/or all alternatively spliced isoforms of hsl. Therefore, the claimed invention lacks enablement for the scope drawn to this broad genus.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11-13, 15, 71-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 11, line 1, the metes and bounds of the term "compound" cannot be determined. Appropriate clarification is requested.

In claim 76, line 1, the metes and bounds of the term "oligonucleotide mimetic compound" cannot be determined. Appropriate clarification is requested.

In claim 81, line 1, "the antisense oligonucleotide" lacks proper antecedent basis. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 11-13, 15, 71-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compounds and oligonucleotide mimetic compounds that target and inhibit the expression of the nucleic acid molecule encoding human hormone sensitive lipase. The specification and claims do not describe the elements that are essential to the genera comprising compounds or oligonucleotide mimetic compounds. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genera comprising either compounds or oligonucleotide mimetic compounds. The scope of the claims includes numerous structural variants and the genera are highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures or compounds within a genus from others are missing from the disclosure. The specification fails to teach or adequately describe a representative number of species in each genera such that the common attributes or characteristics concisely identifying memebers of each proposed genera are exemplified and because each genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably

conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Theus, Applicant was not in possession of the claimed genera.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-8, 11-15, 72-81 are rejected under 35 U.S.C. 102(a) as being anticipated by Mitchell et al.

Mitchell et al (document "AA" provided in the IDS, filed October 19, 2001, Paper No. 4) teach compositions comprising antisense oligonucleotides between 8-50 nucleobases which specifically target and inhibit the expression of SEQ ID NO: 3 in vitro, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O methoxyethyl sugars, and modified nucleobases, and which compositions further comprise a pharmaceutically acceptable carrier and a colloidal dispersion system, which antisense oligonucleotides target and inhibit the expression of SEQ ID NO: 3 in an appropriate target cell, including HepG2 target cells (See entire document, especially page 4, pages 6-8, pages 11-13, and the accompanying sequence alignment data).

Claims 1, 2, 11 and 72-75 are rejected under 35 U.S.C. 102(b) as being anticipated by Holst et al.

Holst et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3, which antisense oligonucleotides target and inhibit the expression of SEQ ID NO: 3 in an appropriate target cell, including HepG2 target cells (See especially the fourth full paragraph on page 442).

Claims 1, 2, 11 and 72-75 are rejected under 35 U.S.C. 102(b) as being anticipated by

Langin et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3, which antisense oligonucleotides target and inhibit the expression of SEQ ID NO: 3 in an appropriate target cell, including HepG2 target cells (See especially second and fourth full paragraphs on page 4898).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-15, 72-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitchell et al, Holst et al and Langin et al as applied to claims 1, 2, 4-8, 11-15, 72-81 above, and further in view of Milner, Baracchini et al and Wright.

The claims are drawn to compositions comprising antisense oligonucleotide compounds between 8-50 nucleotides which specifically target and inhibit, by at least 5%, the expression of human hsl of SEQ ID NO: 3 in HepG2 cells of 80% confluence in vitro, and which oligonucleotides further comprise internucleotide linkage modifications, sugar modifications, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Mitchell et al (document "AA" provided in the IDS, filed October 19, 2001, Paper No. 4) teach compositions comprising antisense oligonucleotides between 8-50 nucleobases which specifically target and inhibit the expression of SEQ ID NO: 3 in vitro, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O methoxyethyl sugars, and modified nucleobases, and which compositions further comprise a pharmaceutically acceptable carrier and a colloidal dispersion system Mitchell et al also teach the participation of hormone sensitive lipase in the process of fertility (See entire document, especially page 4, pages 6-8, pages 11-13, and the accompanying sequence alignment data).

Holst et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3 (See especially the fourth full paragraph on page 442).

Langin et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3 (See especially second and fourth full paragraphs on page 4898).

The primary references of Mitchell et al, Holst et al and Langin et al do not teach chimeric oligonucleotides, nor 5'-methyl cytosine modified nucleobases, nor the inhibition of the target gene hormone-sensitive-lipase of SEQ ID NO: 3 in 80% confluent HepG2 cells in vitro..

Baracchini et al teach the incorporation 5 methyl cytosines and chimeric structures into antisense oligonucleotides for enhancing target binding, cellular uptake and stability of antisense oligonucleotides (see col. 7-8). Baracchini et al also teach the method of assessing antisense inhibition of a target gene in approprate target cells in vitro (see tables 1-4 in columns 10-12).

Milner teaches methods of designing and assessing the ability of antisense to inhibit a target gene of known nucleotide sequence (see entire document, especially pages 538-539).

Wright teaches target gene inhibition in HepG2 target cells in culture using antisense oligonucleotides (see table 13, columns 45-46).

It would have been obvious to one of ordinary skill in the art to generate and assess the ability of antisense oligonucleotides to target and inhibit the expression of the known target gene human hormone sensitive lipase in an appropriate target cell in vitro because Mitchell et al, Holst et al and Langin et al teach the ability of antisense oligonucleotides (8-50 nucleobases in length) to target and inhibit the expression of hormone sensitive lipase in vitro, Langin teaches the nucleotide sequence of human hormone sensitive lipase, and Milner teaches a general method to

design and assess antisense inhibition of a known target gene in vitro. One of ordinary skill in the art would have been motivated to inhibit the target gene hormone sensitive lipase because Mitchell et al teach the inhibition of hormone sensitive lipase as a means of fertility control (male contraception). One of ordinary skill in the art would have been motivated to target the gene of interest for inhibition, and in an appropriate host cell (HepG2), for assessing antisense inhibition in vitro, because antisense inhibition of a target gene is routinely performed in vitro using an appropriate host target cell, as taught previously by Baracchini (see tables 1-4 in columns 10-12), and Wright teaches antisense inhibition of a target gene in vitro utilizing HepG2 target cells (see table 13, columns 45-46 of Wright). The method of target gene inhibition using antisense in HepG2 target cells in culture, therefore, would presumably be similar to inhibiting the target gene using antisense in another appropriate (mammalian) target cell line in culture (e.g. See MPEP 2112.01-2112.02). It would have been obvious to one of ordinary skill in the art to incorporate various modifications into antisense such as internucleotide linkage, nucleobase, or sugar modifications, as well as designing chimeric antisense oligonucleotides, because Baracchini and Mitchell et al had taught previously that such modifications contribute to the stability, cellular uptake and target binding of antisense oligonucleotide compounds. One of ordinary skill in the art therefore would have expected that antisense comprising such modifications would exhibit enhanced stability, cellular uptake and target binding. One of ordinary skill in the art would have been motivated to utilize compositions comprising pharmaceutically acceptable diluents and colloidal dispersion systems, in combination with antisense oligonucleotides, for transfecting

target cells because such compositions had been taught previously by Baracchini et al and one would have expected that such compositions would minimize toxic effects of target cells while enhancing cellular uptake of the antisense oligonucleotides.

Therefore, the invention has a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a

general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

July 25, 2003